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NEUROCOGNITIVE COMPLICATIONS AFTER CARDIOPULMONARY BYPASS: COMPLICATIONS, RISK FACTORS AND PREVENTION STRATEGIES – A COMPREHENSIVE REVIEW

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ABSTRACT

Neurocognitive complications remain a significant challenge following cardiopulmonary bypass (CPB), contributing to increased morbidity and long-term functional impairment. This review aims to summarize the clinical spectrum, underlying mechanisms, and emerging prevention strategies associated with these complications. A structured analysis of recent clinical studies, guidelines, and experimental data was conducted, focusing on neurological outcomes after cardiac surgery.

Clinical manifestations range from acute events such as stroke and postoperative delirium to more subtle impairments described as postoperative cognitive dysfunction. Increasing attention has been given to subclinical brain injury, including silent cerebral infarctions, which may contribute to long-term cognitive decline despite the absence of overt neurological symptoms.

Current evidence indicates that the pathophysiology is multifactorial. The most consistently supported mechanisms include cerebral microembolization, systemic inflammatory response, and impaired cerebral autoregulation, while other processes such as blood–brain barrier disruption and neurodegenerative changes remain less clearly defined.

Despite advances in perioperative care, effective prevention remains challenging due to the complexity and overlap of these mechanisms. Improved understanding of their relative contributions may support the development of targeted strategies to minimize neurological injury. Future research should focus on standardized definitions, improved monitoring, and individualized perioperative management to reduce the burden of neurocognitive complications after CPB.

KEYWORDS

Cardiopulmonary Bypass, Cardiac Surgery, Extracorporeal Circulation, Postoperative Complications, Risk Factors, Prevention Strategies

CITATION

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Introduction

Cardiopulmonary bypass (CPB) has become an indispensable component of contemporary cardiac surgery, enabling increasingly complex procedures with improved survival outcomes; however, its use continues to be associated with a range of neurological and neurocognitive complications that remain a significant clinical concern (Gilbey et al., 2023; Stanley & Sellke, 2023). Despite substantial advancements in surgical techniques, anesthesia, and extracorporeal circulation technology, adverse effects on the central nervous system (CNS) persist and represent an important determinant of both short- and long-term postoperative outcomes (Gilbey et al., 2023).

Neurocognitive disturbances following cardiac surgery are now recognized as a major contributor to postoperative morbidity, particularly in aging populations undergoing increasingly high-risk procedures (Mattimore et al., 2023; Stanley & Sellke, 2023). These complications not only impact immediate recovery but may also have lasting consequences on functional independence, quality of life, and healthcare utilization (Mattimore et al., 2023). The growing clinical and socioeconomic burden associated with these outcomes has led to increased research interest in understanding their underlying causes and potential preventive strategies (Stanley & Sellke, 2023).

A key challenge in this field is the heterogeneity of neurocognitive outcomes and the lack of universally accepted definitions and diagnostic criteria, which complicates both clinical assessment and research comparisons (Evered et al., 2018; Mattimore et al., 2023). Over time, efforts have been made to standardize terminology and improve methodological consistency, particularly in the context of perioperative neurocognitive disorders, although variability in study design and outcome measures remains a significant limitation in the literature (Evered et al., 2018).

The etiology of neurocognitive complications after CPB is widely considered to be multifactorial, involving a complex interaction between patient-related vulnerability and perioperative factors (Gilbey et al., 2023; Stanley & Sellke, 2023). While numerous mechanisms have been proposed, including embolic, inflammatory, and perfusion-related processes, their relative contributions and interactions are not yet fully understood, reflecting the complexity of brain injury in the perioperative setting (Gilbey et al., 2023). This incomplete understanding continues to limit the development of targeted and consistently effective preventive strategies.

In parallel, advances in perioperative monitoring, biomarker research, and surgical technology have generated new opportunities for early detection and potential mitigation of neurological injury (Stanley & Sellke, 2023). However, the clinical translation of these developments remains inconsistent, and many proposed interventions lack robust evidence from large-scale, well-designed studies (Stanley & Sellke, 2023). As a result, the prevention and management of neurocognitive complications after CPB continue to represent an area of ongoing investigation and debate.

Given these considerations, a comprehensive and critical synthesis of the current evidence is necessary to better characterize the clinical spectrum of neurocognitive complications, elucidate their underlying mechanisms, and evaluate emerging approaches to risk stratification and prevention. This review aims to provide an updated and comprehensive overview of neurocognitive complications following cardiopulmonary bypass, with particular emphasis on their pathophysiological mechanisms, patient- and procedure-related risk factors, and current strategies for prevention and mitigation. In addition, the review addresses recent technological and clinical advancements that may contribute to improved neurological outcomes in modern cardiac surgery and examines their potential implications for the evolving practice of perioperative and cardiovascular care. Particular attention is given to the identification of key limitations in the existing literature, including methodological heterogeneity and gaps in long-term outcome data, with the aim of outlining priorities for future research and supporting the development of more effective, evidence-based clinical strategies.

Methodology

A comprehensive literature review was conducted to identify and synthesize current evidence regarding complications associated with cardiopulmonary bypass (CPB), their mechanisms, risk factors, and prevention strategies in modern cardiac surgery. Relevant publications were identified through searches of major scientific databases, including PubMed, Scopus, and Google Scholar. The search strategy included combinations of the following keywords and their variants: cardiopulmonary bypass, cardiac surgery, extracorporeal circulation, postoperative complications, risk factors, and prevention strategies.

The review included articles published in English to reflect contemporary clinical practice and technological developments in extracorporeal circulation. Both original research studies and review articles were considered, including randomized controlled trials, observational studies, cohort studies, and meta-analyses focusing on CPB-related complications and postoperative outcomes. Particular attention was given to studies describing neurological, cardiovascular, pulmonary, renal, and hematological complications, as well as mechanisms such as systemic inflammatory response, ischemia–reperfusion injury, and coagulation disturbances.

Additional relevant studies were identified through screening reference lists of selected publications. Articles were included based on their relevance to the objectives of this review, specifically their contribution to understanding CPB-related complications, associated risk factors, and preventive strategies used in contemporary cardiac surgery. The collected literature was subsequently analysed and synthesized to provide an integrated overview of current knowledge and recent developments in this field.

Clinical Features

Neurocognitive complications following cardiopulmonary bypass (CPB) constitute a heterogeneous spectrum of clinical manifestations, encompassing acute focal neurological injury, transient neuropsychiatric syndromes, and long-term cognitive impairment, reflecting the complex and multifactorial effects of cardiac surgery on the central nervous system (CNS) (Gilbey et al., 2023; Stanley & Sellke, 2023).

Stroke remains the most severe neurological complication associated with CPB and typically presents with focal deficits such as hemiparesis, aphasia, or visual disturbances, contributing significantly to perioperative morbidity and mortality (Ferrante et al., 2023). The incidence of clinically overt stroke in adult cardiac surgery is generally reported between 1% and 5%, although this varies depending on procedural complexity and patient-related risk factors (Ferrante et al., 2023; Wahba et al., 2025). Beyond clinically evident events, diffusion-weighted magnetic resonance imaging (DW-MRI) studies have demonstrated a markedly higher incidence of silent cerebral infarctions, reported in up to 40–70% of patients undergoing cardiac surgery. These covert lesions have been associated with subsequent neurocognitive decline and reduced quality of life, although the strength of this association remains limited by the predominantly observational design of available studies and incomplete long-term neuropsychological follow-up (Lewis et al., 2021).

Postoperative delirium (POD) represents one of the most frequent neurocognitive complications after CPB and is characterized by an acute and fluctuating disturbance in attention, awareness, and cognition, typically occurring within the first 24–72 hours postoperatively (Mattimore et al., 2023; Stanley & Sellke, 2023). Clinically, delirium may present in hyperactive, hypoactive, or mixed forms, with hypoactive delirium frequently underdiagnosed due to its less overt clinical presentation (Mattimore et al., 2023). The reported incidence of POD after cardiac surgery ranges from approximately 20% to over 50%, depending on diagnostic criteria, patient population, and assessment methodology (Aldecoa et al., 2024; Mattimore et al., 2023). Importantly, POD has been consistently associated with adverse outcomes, including prolonged intensive care unit (ICU) and hospital stay, increased healthcare costs, and higher short- and long-term mortality (Mattimore et al., 2023; Namirembe et al., 2023). Furthermore, emerging evidence suggests an association between postoperative delirium and persistent cognitive decline; however, causality remains uncertain due to potential confounding factors and the limitations of secondary analyses and observational data (Namirembe et al., 2023).

Postoperative cognitive dysfunction (POCD) represents a more subtle yet clinically significant form of neurocognitive impairment, characterized by deficits in memory, attention, executive function, and processing speed that may persist beyond the immediate postoperative period (Stanley & Sellke, 2023; Y. Zhuang et al., 2023). Unlike delirium, POCD typically requires formal neuropsychological testing for diagnosis and is not reliably detectable through routine clinical assessment, contributing to variability in reported incidence rates (Y. Zhuang et al., 2023). Early POCD has been reported in up to 30–60% of patients after cardiac surgery, whereas long-term cognitive impairment persists in approximately 10–30% of individuals months to years following the procedure (Evered et al., 2018; Y. Zhuang et al., 2023). A major limitation of the current literature is the lack of standardized diagnostic criteria and heterogeneity in neuropsychological assessment tools and follow-up intervals, which significantly complicates comparisons between studies (Y. Zhuang et al., 2023). Despite these limitations, POCD has been associated with reduced quality of life, impaired functional independence, and potentially accelerated cognitive aging (Evered et al., 2018).

In addition to overt clinical syndromes, accumulating evidence indicates that CPB is associated with subclinical brain injury, including cerebral microbleeds, white matter lesions, and microembolic phenomena (Condello et al., 2022a; Patel et al., 2019). Cerebral microbleeds, detected using susceptibility-weighted imaging, have been observed in a substantial proportion of patients after cardiac surgery and are thought to reflect microvascular injury related to embolization and hemodynamic instability during CPB (Patel et al., 2019). Intraoperative microembolic signals detected by transcranial Doppler have also been correlated with postoperative cognitive decline, although the strength and consistency of this association vary across studies, and causality remains uncertain (Condello et al., 2022a). The clinical significance of these subclinical findings is still under investigation, as much of the available evidence is derived from observational and exploratory analyses (Condello et al., 2022a; Patel et al., 2019).

The temporal evolution of neurocognitive complications following CPB further underscores their complexity, with different clinical entities manifesting at distinct time points (Stanley & Sellke, 2023). Acute complications such as stroke and delirium typically occur within hours to days after surgery, whereas POCD may develop in the early postoperative period and persist for months or longer (Stanley & Sellke, 2023; Y. Zhuang et al., 2023). This temporal variability suggests that multiple pathophysiological mechanisms including embolic, inflammatory, and perfusion-related factors may contribute differentially over time, although their precise interplay remains incompletely understood (Stanley & Sellke, 2023).

Mechanisms

The pathophysiology of neurocognitive complications following cardiopulmonary bypass (CPB) is complex and multifactorial, involving an interplay of embolic phenomena, systemic and neuroinflammation, cerebral hypoperfusion and dysregulation of autoregulation, blood–brain barrier (BBB) disruption, and metabolic as well as neurodegenerative processes (Gilbey et al., 2023; Stanley & Sellke, 2023).

One of the most extensively studied mechanisms is cerebral microembolization, which occurs as a result of gaseous and particulate emboli generated during CPB from sources such as aortic manipulation, cardiotomy suction, and the extracorporeal circuit is a known source of embolic (Ferrante et al., 2023; Gilbey et al., 2023). These emboli can occlude small cerebral vessels, leading to ischemic injury that may manifest clinically as stroke or remain subclinical as silent infarctions detected on diffusion-weighted imaging (Ferrante et al., 2023; Lewis et al., 2021). Intraoperative transcranial Doppler studies have demonstrated a high burden of microembolic signals during CPB, and several studies suggest an association between embolic load and postoperative cognitive decline, although this relationship is not consistently observed across all cohorts. This inconsistency likely reflects heterogeneity in study design, emboli characterization, and neurocognitive assessment methods (Condello et al., 2022a).

Systemic inflammatory response induced by CPB represents another central mechanism contributing to neurocognitive injury (Ferreira et al., 2023; Gilbey et al., 2023). Contact of blood with artificial surfaces of the extracorporeal circuit activates complement pathways, leukocytes, and cytokine cascades, leading to a systemic inflammatory response syndrome (SIRS) (Ferreira et al., 2023). Pro-inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein have been shown to increase during and after CPB and are associated with neuroinflammatory processes and neuronal injury (Ferreira et al., 2023; Kok et al., 2017). Neuroinflammation may further exacerbate neuronal dysfunction through microglial activation and oxidative stress, although direct causal pathways remain incompletely established in human studies (Kok et al., 2017).

Cerebral hypoperfusion and impaired autoregulation during CPB also play a critical role in the development of neurocognitive complications (Stanley & Sellke, 2023; Vu et al., 2024). Fluctuations in mean arterial pressure (MAP), non-pulsatile flow, and hemodilution can compromise cerebral blood flow, particularly in vulnerable regions such as watershed areas (Vu et al., 2024). Impaired cerebral autoregulation during CPB has been associated with both delirium and postoperative cognitive dysfunction, suggesting that inadequate maintenance of optimal perfusion pressure may contribute to neuronal injury (Brown et al., 2019). Conversely, excessive perfusion leading to cerebral hyperperfusion has also been implicated in delayed neurocognitive recovery, highlighting the importance of maintaining individualized perfusion targets (Kasputytė et al., 2023).

Disruption of the blood–brain barrier (BBB) is increasingly recognized as a key mechanism linking systemic inflammation and cerebral injury (Abrahamov et al., 2017; Ferreira et al., 2023). CPB-related inflammatory processes, along with ischemia–reperfusion injury, can increase BBB permeability, allowing circulating cytokines, immune cells, and potentially neurotoxic substances to enter the brain parenchyma. This process may contribute to cerebral edema, neuronal dysfunction, and the development of delirium and cognitive impairment, although direct clinical evidence remains limited and is largely derived from experimental and translational studies (Abrahamov et al., 2017)

Another important mechanism involves cerebral oxygen imbalance, including both hypoxia and impaired oxygen utilization at the tissue level (Stanley & Sellke, 2023; Wang et al., 2022). Studies have demonstrated that intraoperative decreases in regional cerebral oxygen saturation are associated with an increased risk of postoperative cognitive dysfunction and delirium (Wang et al., 2022). Hypoxic injury may be particularly relevant in metabolically active regions such as the hippocampus, where experimental models have shown vulnerability of the CA3 region to hypoxia-induced neuronal damage following CPB (Liu et al., 2022). However, the translation of these findings from animal models to human clinical outcomes remains an area of ongoing investigation (Liu et al., 2022).

Emerging evidence also suggests a potential link between CPB and neurodegenerative processes, including amyloid-beta metabolism and tau pathology (Požgain et al., 2022; Stanley & Sellke, 2023). Elevated levels of beta-amyloid peptides have been observed in some patients following cardiac surgery and have been associated with postoperative cognitive decline, raising the possibility that CPB may accelerate neurodegenerative pathways similar to those seen in Alzheimer's disease. Nevertheless, current evidence is limited and largely exploratory, and a direct causal relationship has not been definitively established (Požgain et al., 2022).

Finally, metabolic and biochemical disturbances during CPB, including glucose dysregulation, oxidative stress, and mitochondrial dysfunction, may further contribute to neuronal injury (Ferreira et al., 2023). These processes can impair cellular energy production and promote apoptosis, thereby exacerbating both acute and long-term neurocognitive impairment (Y. Zhuang et al., 2023). However, many of these mechanisms are supported primarily by experimental or small clinical studies, highlighting the need for further large-scale, mechanistic investigations in human populations.

Overall, neurocognitive complications after CPB arise from a complex interaction of multiple overlapping mechanisms rather than a single dominant pathway, and their relative contribution likely varies depending on patient characteristics, surgical factors, and perioperative management strategies (Gilbey et al., 2023; Stanley & Sellke, 2023).

Risk Factors

The development of neurocognitive complications following cardiopulmonary bypass (CPB) is strongly influenced by a complex interplay of preoperative, intraoperative, and postoperative risk factors, which together determine individual vulnerability to cerebral injury and cognitive decline (Gilbey et al., 2023; Stanley & Sellke, 2023).

Advanced age is consistently identified as one of the most significant and independent risk factors for both postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), likely reflecting reduced cerebral reserve, increased burden of cerebrovascular disease, and age-related neurodegenerative changes (Ferrante et al., 2023; Stanley & Sellke, 2023). Studies have demonstrated that elderly patients, particularly those over 65–70 years of age, exhibit a markedly higher incidence of delirium and persistent cognitive impairment following cardiac surgery, although the precise contribution of age versus comorbidities remains difficult to disentangle due to confounding factors in observational studies (N. Chen et al., 2024; Ferrante et al., 2023).

Pre-existing cognitive impairment and neuropsychiatric conditions, including mild cognitive impairment, dementia, depression, and anxiety, have also been strongly associated with an increased risk of postoperative neurocognitive complications (Gilbey et al., 2023; Stanley & Sellke, 2023). Patients with baseline cognitive deficits may have diminished compensatory mechanisms, making them more susceptible to perioperative insults such as hypoperfusion, inflammation, and embolic injury. However, the strength of these associations is limited by variability in preoperative cognitive assessment and underdiagnosis of subtle impairments in routine clinical practice (Gilbey et al., 2023).

Cardiovascular and systemic comorbidities, including hypertension, diabetes mellitus, atrial fibrillation, and prior cerebrovascular disease, further contribute to increased risk by promoting underlying vascular pathology and impaired cerebral autoregulation (H. Chen et al., 2021; Ferrante et al., 2023). In particular, a history of stroke or transient ischemic attack has been associated with a significantly elevated risk of perioperative stroke and cognitive decline, likely due to pre-existing structural brain damage and compromised cerebral perfusion (Ferrante et al., 2023). Similarly, chronic kidney disease and systemic inflammation have been implicated as contributing factors, although evidence in these areas remains less consistent and is often derived from heterogeneous cohort studies (H. Chen et al., 2021).

Frailty and reduced functional reserve have emerged as important predictors of adverse neurocognitive outcomes following CPB, particularly in older populations. Frail patients are more vulnerable to perioperative stressors and may exhibit exaggerated inflammatory responses and impaired recovery mechanisms, although the lack of standardized frailty assessment tools across studies limits the generalizability of these findings (Stanley & Sellke, 2023).

Intraoperative factors play a critical role in modulating the risk of neurocognitive complications, particularly those related to cerebral perfusion and embolic load. Prolonged duration of CPB and aortic cross-clamping has been consistently associated with increased risk of both delirium and POCD, likely reflecting cumulative exposure to non-physiological perfusion, inflammatory activation, and microembolization (Gilbey et al., 2023; Kumar et al., 2026). Additionally, fluctuations in mean arterial pressure (MAP) and deviations from the patient's autoregulatory range during CPB have been linked to increased incidence of delirium, suggesting that inadequate cerebral perfusion management may contribute to neuronal injury (Brown et al., 2019).

Embolic phenomena remain a key intraoperative risk factor, with aortic manipulation, cannulation techniques, and cardiotomy suction contributing to the generation of gaseous and particulate emboli (Gilbey et al., 2023). Studies using transcranial Doppler have demonstrated that higher intraoperative microembolic burden correlates with an increased risk of postoperative cognitive decline, although the relationship is not

consistently observed across all studies, highlighting methodological variability and potential confounding factors (Condello et al., 2022a).

Anesthetic and pharmacological factors may also influence neurocognitive outcomes, although evidence in this area is mixed. Certain sedative agents and depth of anesthesia have been associated with delirium risk, but findings remain inconsistent due to differences in study design and patient populations (Stanley & Sellke, 2023). For example, some randomized controlled trials suggest that dexmedetomidine may reduce the incidence of delirium, whereas others report no significant effect, indicating ongoing uncertainty regarding optimal anesthetic strategies (X. Zhuang et al., 2024).

Postoperative factors, particularly those related to critical care management, further contribute to neurocognitive risk (Gilbey et al., 2023). Prolonged mechanical ventilation, infection, metabolic disturbances, and sleep disruption have all been associated with increased incidence of delirium and delayed cognitive recovery (N. Chen et al., 2024; Gilbey et al., 2023). Additionally, postoperative complications such as atrial fibrillation and hemodynamic instability may exacerbate cerebral hypoperfusion and embolic risk, thereby contributing to secondary brain injury (N. Chen et al., 2024).

Biomarkers have been increasingly investigated as predictors of neurocognitive complications, with proteins such as S100B, neuron-specific enolase (NSE), and natriuretic peptides showing potential associations with postoperative delirium and cognitive decline (Barbu et al., 2022; Ji & Li, 2022). Elevated levels of these biomarkers may reflect neuronal injury, blood–brain barrier disruption, or systemic stress responses; however, their clinical utility remains uncertain due to inconsistent findings, lack of standardized thresholds, and limited validation in large prospective studies (Barbu et al., 2022). Consequently, current evidence regarding biomarkers should be interpreted with caution, as much of it remains exploratory and not yet applicable to routine clinical practice (Ji & Li, 2022).

Importantly, the interaction between multiple risk factors appears to be more predictive of neurocognitive outcomes than any single variable alone (Gilbey et al., 2023; Stanley & Sellke, 2023). Multimodal risk models incorporating demographic, clinical, and intraoperative parameters have shown promise in identifying high-risk patients, although their predictive accuracy varies and external validation is often lacking (Gilbey et al., 2023). This highlights a critical gap in the literature and underscores the need for standardized, large-scale studies to better define and quantify risk profiles in patients undergoing CPB.

Overall, neurocognitive complications after CPB arise from a convergence of patient-related vulnerability and perioperative exposures, with substantial heterogeneity across individuals, emphasizing the importance of personalized risk assessment and targeted preventive strategies (Gilbey et al., 2023; Stanley & Sellke, 2023).

Prevention

Prevention of neurocognitive complications following cardiopulmonary bypass (CPB) remains a major clinical priority, given the multifactorial pathophysiology and the significant impact of these complications on patient outcomes, healthcare costs, and long-term quality of life (Gilbey et al., 2023; Stanley & Sellke, 2023). Current preventive strategies are necessarily multimodal and target different stages of the perioperative period, including optimization of cerebral perfusion, reduction of embolic load, modulation of inflammatory responses, and implementation of neuroprotective monitoring techniques (Gilbey et al., 2023).

Optimization of intraoperative cerebral perfusion represents a cornerstone of neuroprotection during CPB (Stanley & Sellke, 2023). Maintenance of mean arterial pressure (MAP) within the limits of cerebral autoregulation has been associated with a reduced incidence of postoperative delirium, suggesting that individualized perfusion targets may be more effective than fixed pressure strategies (Brown et al., 2019). Continuous monitoring of cerebral autoregulation and regional cerebral oxygen saturation using near-infrared spectroscopy (NIRS) has been increasingly adopted, with several meta-analyses demonstrating an association between intraoperative cerebral desaturation and postoperative cognitive dysfunction (Tian et al., 2022; Wang et al., 2022). However, although NIRS-guided interventions appear promising, evidence remains heterogeneous, and not all studies have demonstrated a clear reduction in clinically significant neurocognitive outcomes, limiting the strength of current recommendations (Tian et al., 2022).

Reduction of intraoperative embolic burden constitutes another key preventive strategy (Gilbey et al., 2023). Technical modifications such as minimized or closed CPB circuits, arterial line filters, and careful aortic manipulation have been shown to reduce the number of microembolic signals detected intraoperatively (Liebold et al., 2006). Miniaturized cardiopulmonary bypass systems, in particular, have been associated with reduced inflammatory activation and improved short-term outcomes, although their specific impact on long-

term neurocognitive function remains incompletely established due to limited follow-up data (Zangrillo et al., 2010). Similarly, the use of biocompatible and heparin-coated circuits has been shown to attenuate inflammatory responses and may contribute indirectly to neuroprotection, although evidence linking these strategies directly to improved cognitive outcomes is still limited (Videm et al., 1999).

Temperature management during CPB has also been extensively investigated as a neuroprotective strategy (Gilbey et al., 2023). Mild hypothermia has traditionally been used to reduce cerebral metabolic demand; however, recent systematic reviews suggest that the benefits of targeted temperature management on postoperative cognitive outcomes are inconsistent, with some studies showing no significant advantage compared to normothermia. This inconsistency may reflect heterogeneity in temperature protocols, patient populations, and outcome definitions, highlighting the need for standardized approaches in future studies (Linassi et al., 2022).

Pharmacological interventions aimed at neuroprotection have yielded mixed results and remain an area of active investigation (Stanley & Sellke, 2023). Dexmedetomidine, a selective α2-adrenergic agonist, has been associated with a reduced incidence of postoperative delirium in several randomized controlled trials and meta-analyses, likely due to its sedative, anti-inflammatory, and sympatholytic properties. However, not all studies have demonstrated consistent benefit, and variability in dosing regimens and patient populations limits generalizability (X. Zhuang et al., 2024). Other agents, including lidocaine, ketamine, magnesium, and various anesthetic techniques, have been evaluated, but evidence supporting their routine use for neuroprotection remains inconclusive, with many studies showing neutral or inconsistent effects on cognitive outcomes (Klinger et al., 2016; Mathew et al., 2013).

Inflammation-modulating strategies have also been explored, given the central role of systemic inflammatory response in CPB-related brain injury (Gilbey et al., 2023). Interventions such as ultrafiltration, corticosteroids, and antioxidant therapies (e.g., vitamin C) have shown potential in reducing inflammatory markers; however, their impact on neurocognitive outcomes remains uncertain and is often based on small or single-center studies with limited external validity (Kuribayashi et al., 2025). As a result, these approaches cannot yet be considered standard of care for neuroprotection.

Perioperative management strategies, particularly those targeting delirium prevention, have gained increasing attention. Implementation of standardized delirium prevention protocols including early mobilization, optimization of sleep, minimization of sedative exposure, and effective pain control has been associated with reduced incidence of postoperative delirium in general surgical populations and is increasingly recommended in cardiac surgery settings (Stanley & Sellke, 2023). Nevertheless, high-quality evidence specific to CPB patients remains limited, and extrapolation from non-cardiac populations should be interpreted cautiously.

Emerging technologies and monitoring strategies offer additional avenues for prevention (Gilbey et al., 2023). Advanced neuromonitoring techniques, including processed electroencephalography (EEG) and cerebral autoregulation monitoring, may allow for real-time optimization of anesthetic depth and cerebral perfusion, potentially reducing the risk of delirium and cognitive dysfunction (Milne et al., 2022). Furthermore, intraoperative detection and mitigation of microembolic signals using specialized filtration systems and circuit designs represent a promising area of research, although robust clinical outcome data are still lacking (Condello et al., 2022b).

Despite these advances, it is important to emphasize that many preventive strategies are supported by heterogeneous or moderate-quality evidence, and definitive conclusions regarding their effectiveness are often limited by variability in study design, outcome definitions, and follow-up duration (Gilbey et al., 2023; Stanley & Sellke, 2023). In particular, long-term neurocognitive outcomes are infrequently assessed, and many studies rely on surrogate markers such as cerebral oxygenation or biomarker levels rather than clinically meaningful endpoints.

Overall, prevention of neurocognitive complications after CPB requires a comprehensive and individualized approach that integrates patient risk stratification with targeted intraoperative and postoperative interventions (Gilbey et al., 2023). Future research should focus on large-scale, well-designed randomized trials with standardized neurocognitive assessments to better define the effectiveness of preventive strategies and to facilitate their translation into clinical practice.

Discussion

Neurocognitive complications following cardiopulmonary bypass (CPB) represent a persistent and clinically significant challenge despite substantial advances in cardiac surgery and perioperative care, reflecting the complex and multifactorial nature of perioperative brain injury (Gilbey et al., 2023; Stanley & Sellke, 2023). The findings summarized in this review indicate that these complications encompass a broad spectrum of clinical manifestations, ranging from overt neurological events to more subtle and frequently underdiagnosed cognitive impairments, which together contribute to increased morbidity and long-term functional decline (Gilbey et al., 2023).

A central observation emerging from the current literature is the lack of a single dominant mechanism responsible for neurocognitive injury after CPB, with evidence supporting the involvement of multiple overlapping pathways, including embolic phenomena, inflammatory responses, and disturbances in cerebral perfusion (Gilbey et al., 2023; Stanley & Sellke, 2023). Although each of these mechanisms has been independently associated with adverse neurological outcomes, their relative contribution appears to vary between patients and clinical contexts, complicating efforts to establish clear causal relationships. Furthermore, much of the mechanistic evidence is derived from observational studies or experimental models, limiting the ability to draw definitive conclusions regarding causality in human populations.

Similarly, the identification of risk factors has improved our understanding of patient susceptibility; however, predictive models remain imperfect and are often limited by heterogeneity in study populations and outcome definitions (H. Chen et al., 2021; Stanley & Sellke, 2023). While factors such as advanced age, pre-existing cognitive impairment, and comorbidities are consistently associated with increased risk, their integration into clinically useful risk stratification tools is still evolving. In addition, interactions between preoperative vulnerability and intraoperative exposures appear to be critical, yet are not fully captured in current predictive frameworks.

Preventive strategies have shown variable success, highlighting both progress and ongoing uncertainty in this field (Gilbey et al., 2023; Stanley & Sellke, 2023). Approaches targeting cerebral perfusion optimization, embolic load reduction, and neuromonitoring have demonstrated potential benefits, but the overall strength of evidence remains moderate and often inconsistent across studies. Notably, many interventions are supported by surrogate endpoints, such as cerebral oxygenation or biomarker levels, rather than robust long-term neurocognitive outcomes, limiting their clinical applicability. Pharmacological strategies, although promising in selected contexts, have likewise produced heterogeneous results, underscoring the need for further high-quality randomized controlled trials.

An important limitation across the literature is the lack of standardized definitions and assessment methods for neurocognitive outcomes, particularly in the context of postoperative cognitive dysfunction (POCD) (Evered et al., 2018). Variability in neuropsychological testing protocols, timing of assessments, and diagnostic criteria significantly complicates comparisons between studies and may contribute to discrepancies in reported incidence rates. Although recent efforts to standardize nomenclature represent a step forward, their implementation remains inconsistent in clinical research.

Another critical gap relates to the limited availability of long-term follow-up data, which restricts understanding of the persistence and clinical relevance of neurocognitive changes after CPB (Stanley & Sellke, 2023). While short-term outcomes such as delirium are relatively well characterized, the trajectory of cognitive recovery or decline over months to years remains insufficiently defined. This limitation is further compounded by the influence of aging and comorbid conditions, which may confound the attribution of long-term cognitive changes to surgical factors alone.

Emerging areas of research, including biomarker development and advanced neuromonitoring techniques, offer promising avenues for improving early detection and risk stratification (Gilbey et al., 2023). However, these approaches are still largely investigational, and their integration into routine clinical practice is constrained by limited validation and lack of standardized thresholds. Additionally, growing interest in the potential link between CPB and neurodegenerative processes highlights the need for interdisciplinary research bridging cardiac surgery, neurology, and cognitive science, although current evidence in this area remains exploratory.

Overall, the current body of evidence underscores the need for a more integrated and methodologically rigorous approach to the study of neurocognitive complications after CPB. Future research should prioritize large-scale, multicenter studies with standardized outcome measures, comprehensive pre- and postoperative cognitive assessments, and extended follow-up periods. Such efforts will be essential to clarify causal mechanisms, refine risk prediction, and establish effective, evidence-based preventive strategies.

Conclusions

Neurocognitive complications following cardiopulmonary bypass constitute a clinically significant and consistently observed consequence of cardiac surgery, encompassing both acute and long-term disturbances that impact patient recovery and functional outcomes (Gilbey et al., 2023; Stanley & Sellke, 2023). Current evidence clearly indicates that these complications are not incidental but represent an integral component of perioperative risk, particularly in vulnerable patient populations.

The available literature supports the concept that neurocognitive injury after CPB arises from a multifactorial process involving embolic load, inflammatory activation, and disturbances in cerebral perfusion, with no single mechanism fully accounting for the observed clinical heterogeneity (Gilbey et al., 2023). Importantly, these mechanisms appear to act synergistically rather than independently, suggesting that effective prevention requires a multimodal rather than isolated approach.

From a clinical perspective, several factors have been consistently associated with increased risk, including advanced age, pre-existing cognitive impairment, and perioperative hemodynamic instability, supporting the need for routine risk stratification in patients undergoing cardiac surgery (Stanley & Sellke, 2023). In parallel, intraoperative strategies aimed at maintaining cerebral perfusion within autoregulatory limits and reducing embolic burden represent rational and increasingly supported approaches to neuroprotection, even though their impact on long-term cognitive outcomes remains incompletely quantified.

While numerous preventive interventions have been proposed, the most robust evidence currently supports the use of individualized perfusion management and multimodal perioperative care strategies, particularly those targeting delirium prevention (Stanley & Sellke, 2023). In contrast, pharmacological neuroprotection and biomarker-guided approaches remain promising but insufficiently validated for routine clinical implementation.

Despite ongoing uncertainties, a key practical implication of current knowledge is that neurocognitive complications after CPB should be regarded as, at least in part, potentially modifiable rather than inevitable. This perspective shifts the focus toward proactive perioperative management, integrating patient-specific risk assessment with targeted intraoperative and postoperative interventions.

Future research should aim not only to clarify mechanisms but also to translate existing knowledge into standardized clinical protocols, with particular emphasis on long-term cognitive outcomes and patient-centered measures. Greater methodological consistency and large-scale prospective studies will be essential to refine current strategies and improve their effectiveness.

In summary, although important gaps in knowledge remain, substantial progress has been made in understanding the determinants of neurocognitive complications after CPB, and current evidence supports the implementation of integrated, multimodal approaches to reduce their incidence and impact in clinical practice.

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